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Cardiovascular adjustments to acute hypoxemia superimposed on chronic hypoxemia in lambs

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Dalinghaus, Michiel, Jan Willem C. Gratama, Willem G. Zijlstra, and Jaap R. G. Kuipers. Cardiovascular adjustments to acute hypoxemia superimposed on chronic hypoxemia in lambs. *Am. J. Physiol.* 268 (*Heart Circ. Physiol.* 37): H974–H979, 1995.—Cardiovascular responses to acute hypoxemia are in part mediated through adrenergic and chemoreceptor stimulation. In chronic hypoxemia the response to these stimuli may be blunted. Therefore, we determined whether the cardiovascular responses to acute hypoxemia superimposed on 3–4 wk of chronic hypoxemia were blunted in lambs with an experimental cardiac right-to-left shunt (combination of atrial septal defect and variable pulmonary stenosis). Cardiovascular variables and regional blood flows were determined during chronic hypoxemia and after acutely reducing the arterial oxygen saturation by increasing the cardiac right-to-left shunt. Arterial oxygen saturation decreased (65 ± 7 to $40 \pm 7\%$, $P < 0.001$) and systemic blood flow increased (164 ± 63 to 233 ± 100 ml·min⁻¹·kg⁻¹, $P < 0.01$), maintaining systemic oxygen supply and oxygen uptake. Blood flow to the myocardium ($P < 0.01$), the adrenals ($P < 0.05$), and the brain ($0.05 < P < 0.10$) increased, and oxygen supply to these organs was maintained. Conversely, blood flow to the kidneys and the gastrointestinal tract was unaltered, so that oxygen supply to these organs was decreased. The responses to acute hypoxemia in chronically hypoxemic lambs were similar to those previously reported in normoxemic lambs. We conclude that the cardiovascular responses to acute hypoxemia in chronically hypoxemic lambs are not blunted.

cyanotic heart disease; chemoreceptors; regional blood flow; microspheres; myocardial oxygen uptake

ACUTE HYPOXEMIA induces cardiorespiratory responses to maintain an adequate oxygenation of tissues. Heart rate, systemic blood flow, and ventilation all increase, while vascular resistance decreases and systemic blood flow is redistributed (9, 25). These adjustments are the result of local vascular, humoral, and chemoreceptor responses (15). Local vascular responses redistribute blood flow to metabolically active organs (15), adrenergic mechanisms increase heart rate and systemic blood flow (9, 26), and chemoreceptor stimulation induces increased ventilation and heart rate and vasodilation (20, 24).

In chronic hypoxemia other adjustments come into play. Hemoglobin concentration, ventilation, and heart rate are increased, while systemic blood flow is not increased (7, 30); it is, however, redistributed away from nonvital organs (4). Adrenergic mechanisms are less important in chronic hypoxemia: catecholamine concentrations are not uniformly reported to be increased, and adrenergic receptors are downregulated (5, 7, 19). Although chemoreceptor activity may be significant in

chronic hypoxemia (31), the hypoxic sensitivity of peripheral chemoreceptors decreases after prolonged hypoxemia (28, 31). Thus the cardiovascular responses to acute hypoxemia that are mediated through chemoreceptor or adrenergic stimulation may be blunted when acute hypoxemia is superimposed on chronic hypoxemia.

Another factor that may affect the cardiovascular response to acute hypoxemia is the adequacy of myocardial oxygen supply. In a previous study we demonstrated that in chronically hypoxemic lambs, left ventricular oxygen supply was matched to oxygen demand at the expense of the coronary flow reserve (7). During acute hypoxemia left ventricular blood flow, oxygen supply, and oxygen uptake increase, and no signs of a lack of myocardial oxygen are found, even during severe reductions in arterial oxygen saturation (9, 11, 25, 26), so that one may expect that myocardial oxygenation can be well maintained when moderate acute hypoxemia is superimposed on chronic hypoxemia.

In previous studies by Teitel et al. (30), Bernstein et al. (4, 5), and from our laboratory (7), the effects of chronic hypoxemia in lambs, with experimental cyanotic heart disease induced by a combined pulmonary stenosis and atrial septal defect, have been reported. We used this experimental setup to study the adequacy of the cardiovascular responses and of left ventricular oxygenation during acute hypoxemia superimposed on chronic hypoxemia, induced by increasing the cardiac right-to-left shunt. We hypothesized that the cardiovascular responses to acute hypoxemia might be blunted and that left ventricular oxygenation would be adequate.

MATERIALS AND METHODS

Nine lambs of mixed breed underwent surgery before the tenth day of life. These lambs were studied in the sixth week of life after 3–4 wk of hypoxemia.

Surgical procedures and postoperative care. Chronic hypoxemia was produced by creating an atrial septal defect and pulmonary stenosis as previously described (7). A left thoracotomy was performed in the fourth intercostal space under general anesthesia with halothane and with piritramide (given intramuscularly) and lidocaine (given locally) for analgesia before every skin incision. Polyvinyl catheters (1.5 mm OD, 1.0 mm ID) were inserted into the ascending aorta, pulmonary artery, right ventricle, superior vena cava, left atrium, and coronary sinus. Through a hind limb vein a 5-F Fogarty catheter was advanced into the left atrium, via the foramen ovale, and an atrial septostomy was performed. An inflatable silicone rubber constrictor (8–10 mm ID) was placed around the main pulmonary artery. All catheters were tunneled to the left flank and protected in a Teflon pouch that was attached to

the skin. Weekly, the lambs were given iron dextran complex intramuscularly, equivalent to 200 mg of iron.

Induction of hypoxemia was started 3–5 days after surgery. The constrictor around the pulmonary artery was inflated with sterile saline solution (9 g/l), thus inducing an atrial right-to-left shunt through the foramen ovale. On the first and second day of inflation, the right ventricular systolic pressure was raised to systemic and suprasystemic levels, respectively. Thereafter, the constrictor was inflated to lower the arterial oxygen saturation to 60–70%.

Experimental protocol. Measurements were made in a room with a temperature of 19–23°C, while the lamb was at rest. Oxygen uptake was continuously recorded for 30 min. During this period blood pressures were measured every 5 min in the aorta and the left and right atrium. At 15 and 30 min we withdrew blood samples from the aorta, pulmonary artery or right ventricle, and coronary sinus to measure oxygen saturation, hemoglobin concentration, hematocrit, blood gases, and pH. At 30 min additional blood was obtained from the aorta and the coronary sinus to determine lactate concentrations. At the end of this period radiolabeled microspheres were injected into the left atrium, while simultaneously a reference sample was withdrawn from the ascending aorta.

Subsequently, the arterial oxygen saturation was acutely decreased by further inflating the constrictor around the pulmonary artery. We attempted to decrease the arterial oxygen saturation by approximately one-half. After 5–10 min of stabilization, we repeated the measurements as in the control period for 15 min. At 10 and 15 min, blood samples from the ascending aorta, pulmonary artery or right ventricle, and the coronary sinus were withdrawn to measure oxygen saturation, hemoglobin concentration, hematocrit, blood gases, pH, and lactate. After 15 min, organ blood flows were determined by the microsphere method. At the end of the study the lamb was killed by the injection of an overdose of pentobarbital. At autopsy all catheter positions were verified, and organs were taken out to be processed for measurement of radioactivity.

Measurements and calculations. Oxygen uptake was measured by an open flow-through system by means of a Diaferometer MG 4 (Kipp & Zonen, Delft, The Netherlands). Blood pressures were measured by Gould P23-ID transducers (Spectramed, Oxnard, CA). Blood gases and pH were measured on an ABL2 (Radiometer A/S, Copenhagen, Denmark) at 37°C and were corrected to actual body temperature. Oxygen saturation, hemoglobin concentration, and hematocrit were all measured in duplicate: oxygen saturation by an OSM2 (Radiometer A/S), hemoglobin concentration by the cyanomethemoglobin method, and hematocrit by the microhematocrit method. Lactate was measured in triplicate with a NADP/NADPH-linked enzymatic method.

Organ blood flows were determined by the microsphere method (16). Microspheres of 15 μ m diameter labeled with either ^{141}Ce , ^{103}Ru , ^{51}Cr , or ^{95}Nb (NEN-Trac, Du Pont, Wilmington, DE) were used. The reference sample was withdrawn at a rate of 6–7 ml/min with a Harvard pump (Harvard Apparatus, Millis, MA), starting just before and ending at least 45 s after completion of the microsphere injection. Organs that were taken out for measurement of radioactivity were stripped of peri-organ fat, and the contents were removed from hollow organs. The ventricular myocardium was divided into the septum and the right and left ventricular free wall; each ventricular part was separated into an inner, middle, and outer layer. The gastrointestinal tract was divided into esophagus, stomach, small intestine, and large intestine. Radioactivity was measured with a Beckman 9000 multichannel gamma-scintillation counter (Beckman Instruments, Fullerton, CA).

Hepatic arterial blood flow was calculated from the microspheres that lodged in the liver. Total hepatic blood flow was calculated as the sum of hepatic arterial blood flow and portal venous blood flow. Portal venous blood flow was calculated as the sum of blood flows to the stomach, the small and the large intestines, the spleen, and the pancreas. Endocardial-to-epicardial blood flow ratio for both the right and the left ventricular free wall was calculated as the ratio of blood flow per 100 g to the inner and the outer ventricular layer.

The heart rate was calculated from the aortic pressure tracing. The systemic blood flow was calculated by the Fick method from the systemic oxygen uptake and the arteriovenous oxygen difference. The rate pressure product (heart rate \times systolic arterial blood pressure) was calculated as an index of left ventricular oxygen demand. The left ventricular arteriovenous oxygen concentration difference was calculated as the difference between ascending aortic and coronary sinus oxygen concentrations obtained at 30 min. Left ventricular oxygen uptake was calculated as the arterio-coronary sinus oxygen concentration difference times blood flow to the left ventricular free wall.

Statistical analysis. The mean and SD were calculated for each variable. Each lamb served as its own control, and the control measurements were compared with those of acute hypoxemia by means of a paired Student's *t*-test. The significance level was 0.05 for all comparisons.

RESULTS

The lambs were 40 ± 3 days old, weighed 11.7 ± 3.4 kg, and had an arterial oxygen saturation of $65 \pm 7\%$. Determinants of systemic oxygen supply and oxygen uptake and their alterations during superimposed acute hypoxemia are shown in Fig. 1. The arterial oxygen concentration decreased by $37 \pm 10\%$ ($P < 0.001$), while systemic blood flow increased ($41 \pm 33\%$, $P < 0.01$) through statistically nonsignificant increases of both heart rate (148 ± 25 to 182 ± 39 beats/min, $0.05 < P < 0.10$) and left ventricular stroke volume (1.2 ± 0.6 to 1.3 ± 0.5 ml/kg), so that systemic oxygen supply was unaltered. Oxygen uptake was unchanged, while mixed-venous oxygen saturation decreased (35 ± 5 to $18 \pm 6\%$,

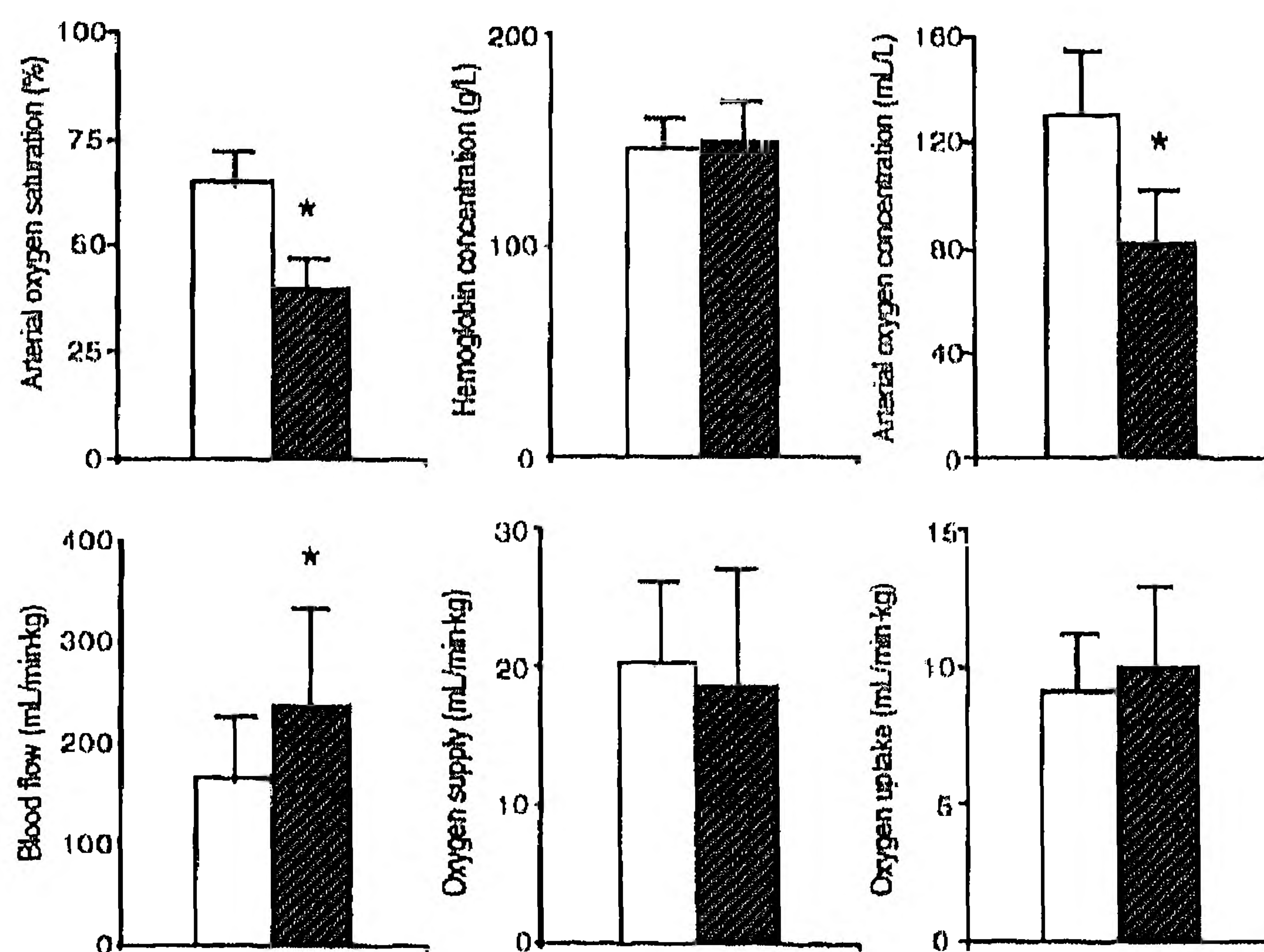


Fig. 1. Systemic oxygen supply and its determinants and oxygen uptake in chronically hypoxemic lambs ($n = 9$) during chronic hypoxemia (open bars) and during acute hypoxemia superimposed on chronic hypoxemia (hatched bars). * $P < 0.05$ by paired *t*-test.

$P < 0.001$) and oxygen extraction increased (45 ± 5 to $56 \pm 8\%$, $P < 0.05$). Blood pressures were unaltered after the induction of superimposed acute hypoxemia, but systemic resistance decreased (Table 1). There were no signs of metabolic acidosis during superimposed acute hypoxemia; the arterial lactate concentration increased twofold, but the increase was not statistically significant (Table 2).

Myocardial and adrenal blood flows increased during superimposed acute hypoxemia, and cerebral blood flow also tended to increase ($28 \pm 36\%$, $0.05 < P < 0.10$), whereas blood flows to other organs did not change (Fig. 2). Endocardial-to-epicardial blood flow ratios decreased for both the left ventricular free wall (1.36 ± 0.17 to 1.24 ± 0.12 , $P < 0.05$) and the right ventricular free wall (1.34 ± 0.10 to 1.17 ± 0.14 , $P < 0.001$). The alterations in organ blood flows corresponded to opposite changes in vascular resistance (Fig. 3): myocardial, cerebral, adrenal, and total resistance decreased significantly. Myocardial, adrenal, and systemic oxygen supply were maintained during superimposed acute hypoxemia, whereas to most other organs it decreased (Fig. 3). Cerebral oxygen supply ranged from 7.3 to 18.4 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ during chronic hypoxemia and was somewhat lower during superimposed acute hypoxemia, but the difference was not statistically significant (Fig. 3). Cerebral oxygen supply was maintained during superimposed acute hypoxemia when cerebral oxygen supply during chronic hypoxemia was 10 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ or lower. In contrast, it decreased when cerebral oxygen supply during chronic hypoxemia was higher than 10 $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$. The decrease in cerebral oxygen supply during superimposed acute hypoxemia was significantly related to the cerebral oxygen supply before the onset of acute hypoxemia (Fig. 4). These results indicate that cerebral oxygen supply decreased during superimposed acute hypoxemia in the lambs with the most luxurious cerebral oxygen supply, whereas it was maintained in the other lambs.

Coronary sinus oxygen saturation decreased (16 ± 6 to $11 \pm 5\%$, $P < 0.001$), and the arterio-coronary sinus oxygen concentration difference decreased by 37% ($P < 0.001$). However, the increase in left ventricular blood flow (Fig. 2) was sufficient to maintain oxygen supply to

Table 2. Blood gases and lactate concentration in the aorta and the coronary sinus

	Control	Acute Hypoxemia
Blood gases and pH		
Arterial		
pH	7.38 ± 0.04	7.37 ± 0.05
PCO_2 , kPa	4.7 ± 0.6	$4.4 \pm 0.6^*$
PO_2 , kPa	7.4 ± 1.1	$5.1 \pm 0.8^\dagger$
Bicarbonate, mmol/l	19.8 ± 3.6	18.5 ± 3.1
Coronary sinus		
pH	7.34 ± 0.02	7.35 ± 0.04
PCO_2 , kPa	5.8 ± 0.2	5.3 ± 0.8
PO_2 , kPa	3.5 ± 1.1	$2.8 \pm 0.6^*$
Bicarbonate, mmol/l	23.5 ± 3.4	20.5 ± 3.6
Lactate, $\mu\text{mol/l}$		
Arterial	$1,315 \pm 192$	$2,701 \pm 927$
Coronary sinus	$1,071 \pm 268$	$2,560 \pm 850$
Arterial - coronary sinus	244 ± 162	142 ± 122

Values are means \pm SD. * $P < 0.05$, $^\dagger P < 0.001$ vs. control.

and oxygen uptake by the left ventricular free wall (747 ± 255 vs. $636 \pm 168 \mu\text{mol} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$). The rate pressure product during superimposed acute hypoxemia was not significantly different from that during chronic hypoxemia (Table 1). There was no net lactate production by the myocardium during superimposed

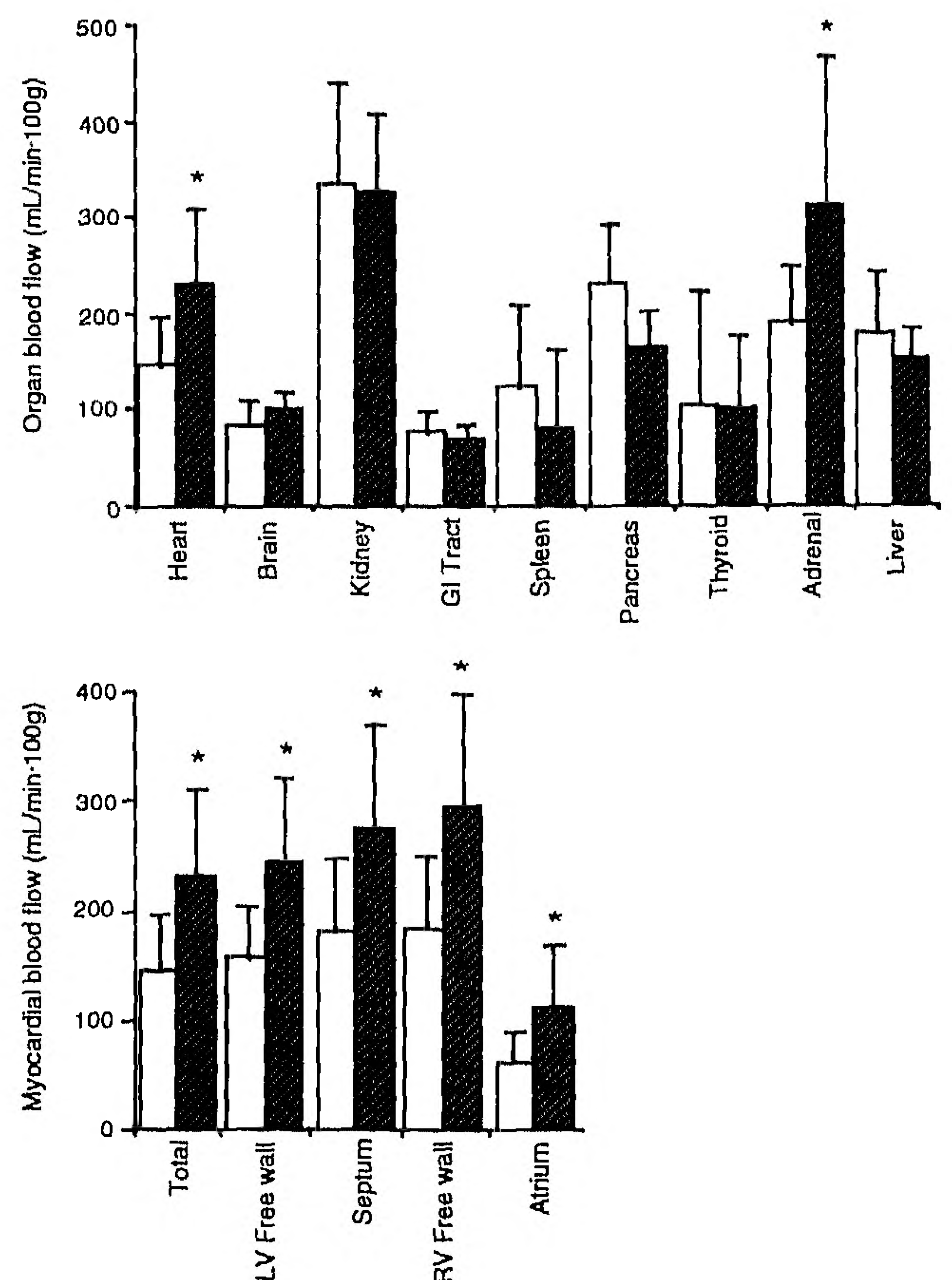


Fig. 2. Blood flow to organs and to myocardial parts in chronically hypoxic lambs (open bars) and during acute hypoxemia superimposed on chronic hypoxemia (hatched bars). LV and RV, left and right ventricular, respectively. $n = 8$ for the brain, and $n = 7$ for the gastrointestinal (GI) tract, liver, spleen, and pancreas. * $P < 0.05$ by paired t -test.

Table 1. Hemodynamic variables

	Control	Acute Hypoxemia
Blood pressure, mmHg		
Arterial		
Systolic	93 ± 7	87 ± 18
Diastolic	65 ± 11	65 ± 14
Mean	76 ± 10	73 ± 11
Right atrial (mean)	4 ± 4	3 ± 4
Left atrial (mean)	4 ± 6	3 ± 4
Systemic resistance, $\text{mmHg} \cdot \text{min} \cdot 100 \text{ g} \cdot \text{ml}^{-1}$	4.9 ± 2.1	$3.6 \pm 2.0^*$
Rate pressure product, $\text{mmHg} \cdot \text{beat}^{-1} \cdot \text{min}^{-1}$	$13,744 \pm 1,951$	$16,003 \pm 5,029$

Values are means \pm SD. Right atrial pressures were obtained in 7 lambs; in the other lambs it was assumed to be 4 mmHg for the calculation of systemic vascular resistance. * $P < 0.001$ vs. control.

acute hypoxemia, and coronary sinus blood gases showed no signs of metabolic acidosis (Table 2).

DISCUSSION

In this study we demonstrate that acute hypoxemia superimposed on 3–4 wk of chronic hypoxemia in lambs leads to an increase in systemic blood flow and a redistribution of blood flow toward vital organs. Consequently, systemic and myocardial blood flow is increased so that systemic and myocardial oxygen supply and oxygen uptake are maintained. In addition, our results strongly suggest that the cardiovascular responses to superimposed acute hypoxemia are adequate to maintain an adequate cerebral oxygenation, although cerebral oxygen supply decreases during superimposed acute hypoxemia in lambs with a more luxurious cerebral oxygen supply.

The cardiovascular adjustments to acute hypoxemia superimposed on chronic hypoxemia in our lambs are quite similar to those described by Sidi et al. (25) for acute hypoxemia in 6-wk-old normoxemic lambs. In that study the arterial oxygen saturation decreased to 45%, similar to the level that was reached in our study, and heart rate and systemic blood flow increased to similar levels as in our lambs. In addition, the pattern of blood flow distribution and the alterations in local vascular

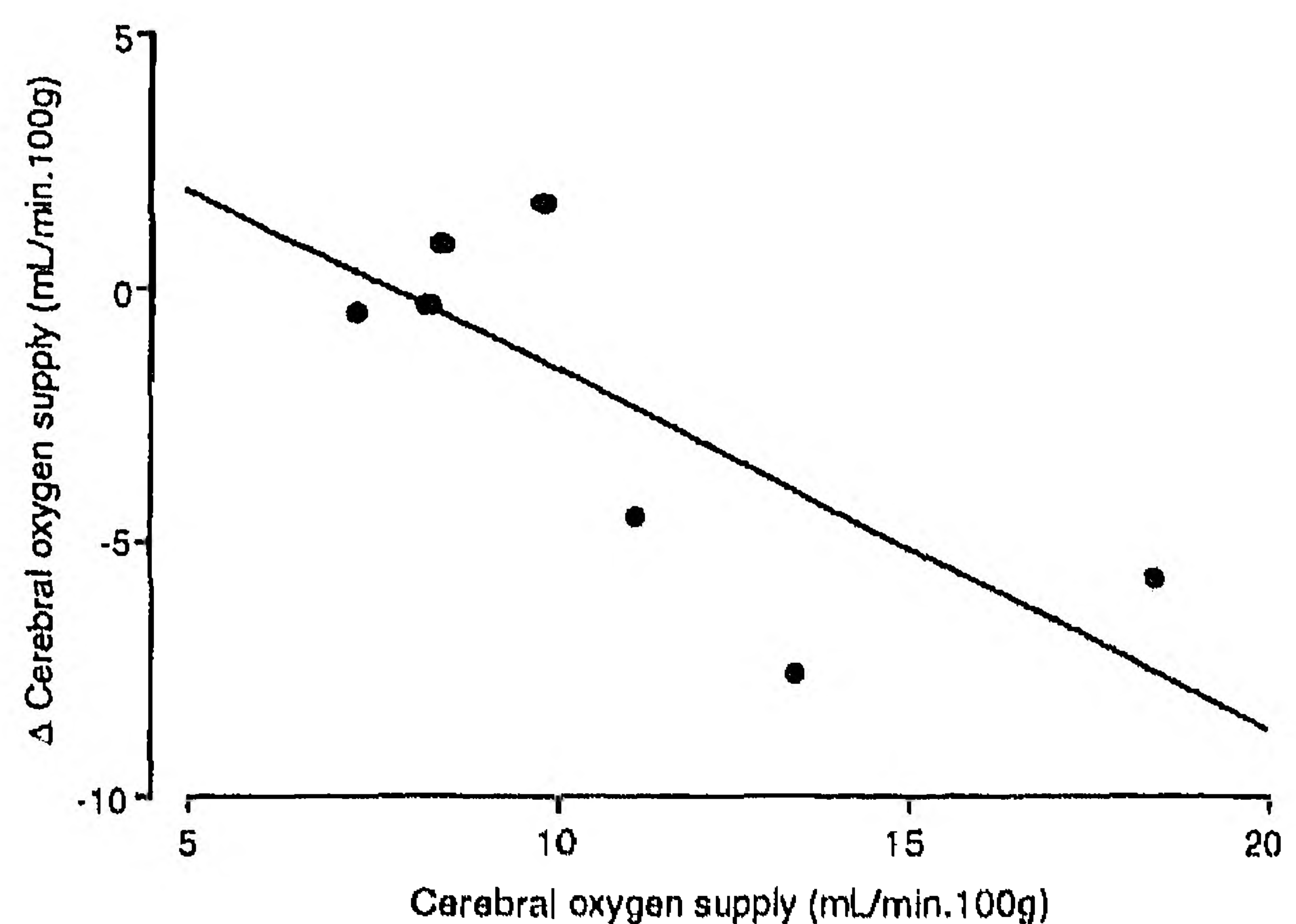


Fig. 4. Change in cerebral oxygen supply during superimposed acute hypoxemia (Δ cerebral oxygen supply) as a function of cerebral oxygen supply before induction of acute hypoxemia. Cerebral oxygen supply during superimposed acute hypoxemia decreased significantly more when the cerebral oxygen supply before induction of acute hypoxemia was higher. Regression: $y = 4.4 - 0.64x$ ($r^2 = 0.51$, $P < 0.05$, $n = 8$).

resistances in that study were also similar to those in our lambs (25).

In acute hypoxemia blood flow to vital organs increases, whereas blood flow to most nonvital organs is maintained (1, 9, 25). Consequently, oxygen supply to vital organs is maintained or increases, whereas to nonvital organs it decreases. In chronic hypoxemia blood flow is also redistributed: blood flow to vital organs is maintained, whereas blood flow to nonvital organs is decreased compared with that in normoxemic control lambs (4), and this is a consequence of the effect of the increased whole blood viscosity in hypoxemic lambs and of vasodilation in vital organs (8). Because the arterial oxygen concentration in chronically hypoxemic lambs is similar to that in normoxemic lambs, oxygen supply to vital organs is maintained in hypoxemic lambs, but to nonvital organs it is decreased as compared with normoxemic lambs (8). The alterations in blood flow, resistance, and oxygen supply of vital organs during superimposed acute hypoxemia in our study suggest that the local vascular responses are unimpaired when acute hypoxemia is superimposed on 3–4 wk of chronic hypoxemia.

Adrenal blood flow increases during acute hypoxemia (9, 21), and epinephrine turnover increases as well (19). The adrenergic response may contribute to the increase in heart rate and systemic blood flow: β -adrenergic blockade during acute hypoxemia abolished the increase in heart rate, systemic blood flow, and oxygen uptake in newborn lambs (26). In contrast, combined α - and β -adrenergic blockade during acute hypoxemia in adult dogs hardly affected the increase in heart rate and in systemic blood flow (9). In our study adrenal blood flow increased during superimposed acute hypoxemia, suggesting adrenergic stimulation. In chronically hypoxemic lambs, left ventricular β -adrenergic receptor density was decreased (5), but the maximal heart rate during catecholamine infusion was similar to that in normoxemic lambs (2). These results suggest that the cardiovascular response to adrenergic stimulation dur-

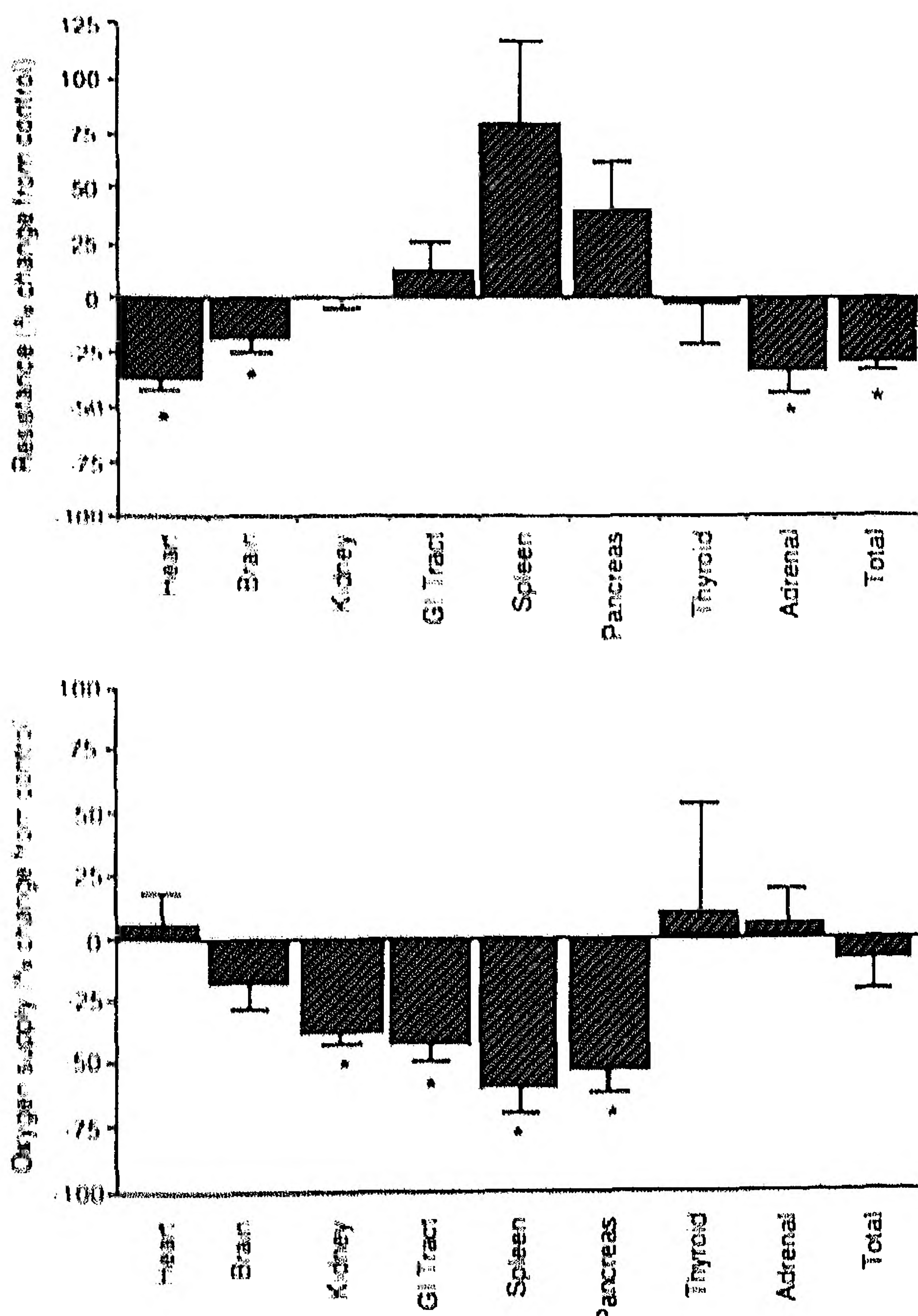


Fig. 3. %Change in resistance and in oxygen supply during acute hypoxemia superimposed on chronic hypoxemia. $n = 8$ for the brain, and $n = 7$ for the GI tract, spleen, and pancreas. * $P < 0.05$ by paired t -test.

ing superimposed acute hypoxemia in our lambs was unimpaired.

The ventilatory response to superimposed acute hypoxemia in the lambs in our study seemed blunted because their arterial PCO_2 hardly decreased, whereas under normal conditions hypocapnic alkalosis develops during acute hypoxemia (9, 25). However, after the induction of superimposed acute hypoxemia, our lambs demonstrated deeper breathing and nasal flaring, suggesting an increased ventilation. This discrepancy may be related to our experimental setup. In most studies, hypoxemia is induced by lowering the inspired oxygen concentration, but in our study hypoxemia was induced by (further) increasing the cardiac right-to-left shunt. We assume that the increase in cardiac right-to-left shunt prevented an appreciable fall in arterial PCO_2 , despite a decrease of the alveolar PCO_2 . Similar observations have been made in exercising humans with a cardiac right-to-left shunt (27). Thus, although only mild hypocapnia developed in the lambs in our study, it does not exclude an adequate ventilatory response. However, taking our experimental setup into account, no meaningful evaluation of the ventilatory response is possible by using the alterations in the arterial blood gases.

One of the hypotheses underlying this study was that chronic hypoxemia attenuates the chemoreceptor-mediated response to acute hypoxemia because of a decreased hypoxic sensitivity (28, 29, 31). Chemoreceptor stimulation induces bradycardia and an increase in systemic vascular resistance, but the subsequent ventilatory response overrides these effects by inducing tachycardia and a decrease in systemic vascular resistance. This sequence of events may explain the decrease in systemic vascular resistance in the lambs in our study after exposure to superimposed acute hypoxemia. In contrast, in animals that are paralyzed and ventilated or are on cardiopulmonary bypass during acute hypoxemia, systemic vascular resistance does not decrease (3, 17). The similarity of the cardiovascular responses to superimposed acute hypoxemia in the lambs in our study to those in normoxemic animals exposed to acute hypoxemia suggests that the chemoreceptor-mediated responses in our lambs were intact. There are several explanations why the hypoxic sensitivity of the chemoreceptors may be unimpaired in the lambs in our study. First, hypoxemia had not been present from birth but was induced between the tenth and fourteenth day of life. By that time chemoreceptors have been reset in lambs (6), and subsequent exposure to hypoxemia may have a different effect on the development of hypoxic sensitivity and its reversibility than if hypoxemia has been present from birth (10, 14). Second, a decrease in hypoxic sensitivity may take longer to develop than 3–4 wk. Although our chronically hypoxemic lambs had an adequate response to superimposed acute hypoxemia, we are not certain that this would have been similar when the period of hypoxemia would have been longer than 3–4 wk.

Left ventricular blood flow was increased during acute hypoxemia superimposed on chronic hypoxemia so that left ventricular oxygen supply and oxygen uptake were

maintained at the same level as during chronic hypoxemia. However, during acute hypoxemia in normoxemic lambs, resulting in a decrease in the arterial oxygen saturation and oxygen concentration comparable to that in the lambs in our study, left ventricular blood flow, oxygen supply, and oxygen uptake all increased (25, 26), indicating an increased oxygen demand. This raises the question whether left ventricular oxygen demand was met during superimposed acute hypoxemia in our lambs. Because left ventricular contractility increases during acute hypoxemia (9) and heart rate was slightly increased in our lambs, one would expect that left ventricular oxygen demand was increased as well. However, the rate pressure product was not significantly increased during superimposed acute hypoxemia in our study. Moreover, we found no evidence of a lack of left ventricular oxygen: there was no net lactate production and there was no metabolic acidosis in the coronary sinus blood during superimposed acute hypoxemia. Although this does not exclude regional differences in lactate production and uptake (22), it suggests that global left ventricular oxygen demand was met. Endocardial-to-epicardial blood flow ratio decreased after the induction of superimposed acute hypoxemia, but the perfusion of the endocardium still was higher than that of the epicardium, also suggesting an adequate perfusion of the most vulnerable part of the myocardium.

In a previous study we demonstrated that left ventricular blood flow in chronically hypoxemic lambs was somewhat increased to meet the increased demand for oxygen (7). We suggested that this was established by some coronary vasodilation and at the expense of the coronary flow reserve to allow for the increase in blood flow and to compensate for the increased whole blood viscosity. The coronary vascular tone in chronically hypoxemic lambs was estimated to be $\sim 70\%$ of that in normoxemic lambs. The increase of left ventricular blood flow during superimposed acute hypoxemia in this study requires a further decrease of the coronary vascular tone to $\sim 35\%$ of that in normoxemic lambs. Similar decrements in coronary vascular tone to allow a three-fold or higher increase in left ventricular blood flow have been found during acute hypoxemia in lambs both before and after birth (23, 25, 26). Thus, although left ventricular oxygen uptake did not increase during superimposed acute hypoxemia, our results suggest that left ventricular oxygen demand was met in these conditions.

To what extent our results can be applied to acute hypoxemia induced by hypoxic spells in subjects with cyanotic congenital heart disease is uncertain. Several pathophysiological mechanisms have been proposed to explain these spells. Increased right-to-left shunting, secondary to increased right ventricular outflow tract obstruction or increased pulmonary vascular resistance (18), a sudden increase of right-to-left shunt secondary to a Valsalva maneuver or its equivalent and hyperpnea (13), and a decrease of systemic vascular resistance (12) all have been suggested as the primary event provoking such a spell. In our experimental setup the primary event was an increase in right ventricular outflow tract obstruction, which is also true for most of the above-

suggested mechanisms. In that respect, the cardiovascular responses that we observed during superimposed acute hypoxemia in our lambs may be quite similar to the responses during a hypoxic spell. However, if a decrease in systemic vascular resistance is the primary event provoking a hypoxic spell, the alterations in local vascular resistances governing the redistribution of blood flow during acute hypoxemia may be different than in our experiment.

In summary, we demonstrated that the cardiovascular responses to acute hypoxemia superimposed on 3–4 wk of chronic hypoxemia in lambs is similar to the responses to acute hypoxemia that have previously been described for normoxemic lambs. In addition, we demonstrated that left ventricular oxygen supply during superimposed acute hypoxemia is adequate to meet left ventricular oxygen demand. Thus the cardiovascular response to acute hypoxemia superimposed on 3–4 wk of chronic hypoxemia in lambs was adequate so that the oxygenation of vital organs could be maintained in these conditions.

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